

Fezolinetant: A novel NK3R antagonist for treating postmenopausal vasomotor symptoms

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Dear Madam, It has been estimated that up to 80% of postmenopausal women experience vasomotor symptoms (VMS) such as hot flushes, night sweats, mood swings and difficulty in concentrating.¹ These symptoms markedly affect different aspects of daily life for women, including, sleep, mental well-being, sex, interpersonal communication and overall quality of life (QOL). Furthermore, they cause a significant burden on healthcare and workplace productivity.

Hormone therapy (HT), involving combined oestrogen and progesterone or oestrogen alone, is the standard management for VMS associated with menopause. However, safety and tolerability issues have discouraged the use of HT, due to the associated risk of breast cancer, stroke and venous thromboembolism.² Alternative treatments, including selective serotonin reuptake inhibitors (SSRIs), clonidine, gabapentin, and herbal remedies, have demonstrated limited effectiveness with undesirable side effects like sedation and nausea.³

This situation warrants a safe and effective non-hormonal therapy for managing menopause-associated VMS. Neurokinin-3 receptor (NK3R) antagonists offer a unique therapeutic approach with minimal adverse effects (AEs). This class of drugs functions by inhibiting the stimulation of KNDy neurons, thereby restoring the normal function of the thermoregulatory centre, which is altered by reduced oestrogen levels and subsequent unopposed action of the neuropeptide neurokinin B on NK3 receptors located on KNDy neurons in the hypothalamus.^{4,5}

In 2023 the United States Food and Drug Administration, has approved the first ever NK3R antagonist, Fezolinetant, (Veoza) for VMS in postmenopausal women. The approval was granted following two phase 3, double-blind placebo controlled trials: SKYLIGHT 1 and 2. The efficacy of the drug was tested for 12 weeks including women aged between 40 and 65 with confirmed menopause and at least 7

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Submission complete: 29-02-2024

Review began: 10-03-2024

Acceptance: 02-05-2024

Review end: 27-04-2024

episodes of hot flushes a day. Vasomotor symptoms, like hot flushes and night sweats, were effectively improved in the control group with beneficial effects on sleep. The most common AE was a headache. Other infrequent and non-serious AEs included abdominal pain, nausea, fatigue and oropharyngeal pain.^{4,5}

NK3R antagonists are an innovative class of drugs that are an effective therapeutic option for postmenopausal symptoms with better efficacy and safety. Availability of the oral form of these drugs makes it an easier option for postmenopausal women, improving overall QOL. The drug's broad coverage of VMS alleviates the need for multiple therapies, decreasing the burden on overall healthcare. Thus, its easy and cost-effective availability in Pakistan is a dire need to combat the challenges faced by postmenopausal women in their daily lives due to undesirable symptoms.

Disclaimer: None.

Conflict of interest: None.

Funding disclosure: None.

DOI: <https://doi.org/10.47391/JPMA.20096>

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Author Contribution:

SA: Conceived, design the analysis and final approval.

MAI: Drafting, editing and revision.